Tetrahedron: *Asymmetry* 23 (2012) 237–239

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Facile conversion of racemic ibuprofen to (*S*)-ibuprofen

David Chavez-Flores *, James M. Salvador †

Department of Chemistry, University of Texas at El Paso, El Paso, TX 79968, USA

ARTICLE INFO

Article history:
Received 9 January 2012
Accepted 23 February 2012

ABSTRACT

The methyl ester of ibuprofen was quantitatively formed by Fischer esterification and converted into (*S*)-ibuprofen in 94% yield with an ee of 94% under dynamic kinetic resolution conditions at pH 9.8, using *Candida rugosa* lipase, and 20% DMSO. The (*R*)-methyl ibuprofen ester was observed to racemize by chiral HPLC without the *Candida rugosa* lipase present. The rates of in situ racemization and enzymatic hydrolysis for the dynamic kinetic resolution were determined to be 0.026 ± 0.004 and $0.053 \pm 0.004\ h^{-1}$, respectively. The rate of enzymatic hydrolysis when no DMSO was present was twice as fast but no racemization occurred. A facile purification of enriched (*S*)-ibuprofen was developed. Overall, 88% of racemic ibuprofen by weight was converted into (*S*)-ibuprofen with an ee of 99.7%.

© 2012 Elsevier Ltd. All rights reserved.

1. Introduction

We recently described a kinetic enzymatic resolution of racemic ibuprofen to isolate 46% (*S*)-ibuprofen (α-methyl-4-[isobutyl] phenylacetic acid) with an enantiomeric excess (ee) of greater than 99% using untreated commercially available *Candida rugosa* lipase.[1] This is significant because (*S*)-ibuprofen is 100 times more active than its (*R*)-enantiomer with fewer side effects.[2] The greater bioactivity of the (*S*)-enantiomer is observed for all members of the profen (2-arylpropionic acid) family of non-steroidal anti-inflammatory drugs (NSAID).[3] In order to overcome the theoretical 50% limit in the resolution of racemic drugs, herein we report the facile conversion of racemic ibuprofen into its (*S*)-enantiomer via unconventional dynamic kinetic resolution conditions.[4,5]

The dynamic kinetic resolution of profens involves the in situ racemization of profen esters in the presence of an enolizing base and a hydrolyzing enzyme in order to drive the equilibrium to isolate mostly (*S*)-profens (Fig. 1). The literature describes several examples of profen esters converted to greater than 50% of (*S*)-profens using encapsulation or membranes in order to protect the activity of the hydrolyzing enzyme (mostly *Candida rugosa* lipase) and a biphasic hydrocarbon/aqueous system.[6,7] The base can be dissolved in either the polar or non-polar layer. The esters vary from the simple methyl ester of naproxen [2-(6-methoxynaphthalen-2-yl) propanoic acid], to the thioesters of fenoprofen [2-(3-phenoxyphenyl)propanoic acid], naproxen, and suprofen [2-[4-(2-thienylcarbonyl)phenyl]propanoic acid] which attempt to mimic the mechanism of the epimerase that is found in the human body.[8]

Noting that (*R*)-ibuprofen is more easily racemized in refluxing base in the presence of dimethylsulfoxide (DMSO), and that up to 20% DMSO by volume neutral aqueous solutions do not hinder *Candida rugosa* lipase activity but actually enhance its enantioselectivity, we investigated the effect of DMSO on the dynamic kinetic resolution of the methyl ester of ibuprofen.[9–11] The use of DMSO to slightly increase (2%) the conversion of racemic 2-ethoxyethyl ibuprofen esters into (*S*)-ibuprofen treated with *Candida rugosa* lipase under dynamic kinetic resolution conditions has also been reported.[12,13]

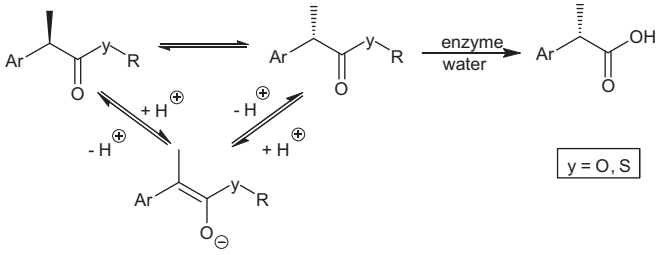

Figure 1. Dynamic kinetic resolution of racemic profen esters.

2. Results and discussion

Without DMSO, under alkaline buffer conditions, no in situ racemization of the methyl ibuprofen ester occurred but most of the (*S*)-methyl ibuprofen ester was enzymatically hydrolyzed in less than 24 h.[14] With a base and DMSO, but no lipase, the methyl ester of (*R*)-ibuprofen was observed to completely racemize in 5 days by chiral HPLC. With DMSO and a base, but before adding

* Corresponding author. Tel.: +1 915 239 0673.
E-mail addresses: dabidcha@hotmail.com, dchavez3@miners.utep.com (D. Chavez-Flores), jsal@utep.edu (J.M. Salvador).
† Tel.: +1 915 747 5704.

0957-4166/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2012.02.014

the lipase, the ester was observed to partially dissolve in the aqueous buffer, which allowed for its more effective contact with the enolizing base. Unlike the previously reported dynamic kinetic resolutions of profens, a biphasic solvent system was not necessary.

Without DMSO, the enantiomeric ratio (E) for the enzymatic hydrolysis was calculated to be 54. Assuming pseudo first-order kinetics [time vs the natural log of the (S)-ibuprofen produced] the rate of enzymatic hydrolysis was about $0.098 \pm 0.001\ h^{-1}$. The rate was the same under neutral or alkaline pH conditions, which indicates that a pH of 9.8 did not have an adverse effect on the lipase and that, unlike previously reported dynamic kinetic resolutions of profens, no special preparation of the lipase was necessary.

'Consecutive reactions with a reversible step' kinetics were fit to the conversion of the racemic methyl ibuprofen ester to (S)-ibuprofen under dynamic kinetic resolution conditions by the least-squares criterion. By this model, the rate of in situ racemization between methyl ester enantiomers catalyzed by base and DMSO was $0.026 \pm 0.004\ h^{-1}$, k_1 and k_{-1} and the rate of enzymatic hydrolysis of the (S)-methyl ibuprofen ester was $0.053 \pm 0.004\ h^{-1}$, k_2 in Figure 2. This indicates that although the base and DMSO did not have an effect on the enzyme separately, together the lipase activity was reduced in half to enable the ester to be racemized.

3. Conclusion

Combining the dynamic kinetic resolution and purification steps, and considering that forming the racemic methyl ester is quantitative, the overall conversion of racemic ibuprofen to pure (S)-ibuprofen was 88%. The application of this methodology to other profens is currently in progress.

4. Experimental

4.1. Materials

Racemic ibuprofen was isolated from inexpensive commercial tablets (200 mg Member's Mark, Sam's Club). *Candida rugosa* lipase (706 units/mg solid) was purchased from Sigma Chemical Company and was used without any further treatment. All other reagents were from commercial sources.

4.2. Analytical methods

4.2.1. Chiral high performance liquid chromatography

All reactions were monitored by chiral HPLC at room temperature with a Chiracel OJ chiral column (Diacel Chemical Industries, Ltd.) capable of resolving racemic ibuprofen, but not the less polar ibuprofen esters. The mobile phase used was hexanes/isopropanol (95:5, v:v) at a flow rate of 1 mL/min. The UV detector was set at 256 nm.

4.3. Procedures

4.3.1. Fischer esterification of ibuprofen

To a 100 mL round bottomed flask was added 40 mL (1 mol) of methanol, 10 mmol of racemic ibuprofen, and 0.5 mL (9 mmol) of concentrated H_2SO_4. The mixture was stirred at 40 °C. By chiral HPLC, after 5 h, all ibuprofen was converted into the ester. The mixture was extracted with 2×40 mL of hexane, and the volatiles were removed on a rotary evaporator to give 2.2 g (10 mmol, quantitative) of the racemic methyl ibuprofen ester. The synthesis of the same ester via its acyl chloride was achieved with less than quantitative yield.

4.3.2. Kinetic resolution of racemic methyl ibuprofen ester at pH 9.8

To a 125 mL round bottomed flask were added 40 mL of pH 9.8 aqueous buffer (100 mL of 0.5 M $NaHCO_3$ + 15.2 mL of 1.0 M NaOH), 2.2 g (10 mmol) of racemic methyl ibuprofen ester, and 1.67 g of *Candida rugosa* lipase.[15] The mixture was stirred at 40 °C and monitored by chiral HPLC for 144 h. The reaction was acidified to pH 5 with 1 M HCl. The mixture was extracted with 2×40 mL of hexanes. The hexanes layers were extracted with 10 mL of 0.5 M NaOH and evaporated to give 1.19 g (5.3 mmol, 53% yield) of enriched (R)-methyl ibuprofen ester.

4.3.3. Racemization of (*R*)-methyl ibuprofen ester with DMSO and base

To a 25 mL round bottomed flask were added 8 mL of pH 9.8 aqueous buffer, 2 mL of DMSO, and 1.1 g (5 mmol) of enriched (R)-methyl ibuprofen ester. The mixture was stirred at 40 °C and monitored by chiral HPLC for 144 h.

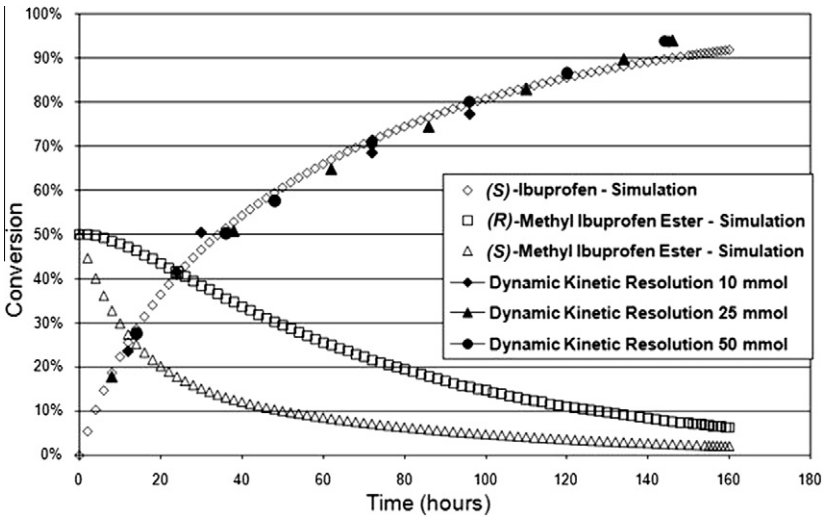

Figure 2. Dynamic kinetic resolution data and consecutive reactions with a reversible step simulation.

4.3.4. Dynamic kinetic resolution of racemic methyl ibuprofen ester

To a 125 mL round bottomed flask was added 32 mL of pH 9.8 aqueous buffer, 8 mL of DMSO, 2.2 g (10 mmol) of racemic methyl ibuprofen ester, and 1.67 g of *Candida rugosa* lipase. The mixture was stirred at 40 °C and monitored by chiral HPLC for 144 h. The reaction was acidified to pH 5 with 1 M HCl. The mixture was extracted with 2 × 40 mL of hexane. The hexane layers were extracted with 20 mL of 0.5 M NaOH. The aqueous layer was acidified to pH 5 with 1 M HCl and extracted with 2 × 40 mL of hexanes. The hexanes were evaporated to give 1.94 g (9.4 mmol, 94% yield) of (*S*)-ibuprofen with an ee of 94%.

4.3.5. Purification of enriched (*S*)-ibuprofen

To a 25 mL round bottomed flask were added 2.00 g (9.7 mmol) of pulverized enantiomerically enriched (*S*)-ibuprofen (ee = 94%) and 10 mL of methanol. The flask was placed in a water bath at 45 °C and stirred with a magnetic bar until of the all ibuprofen had dissolved. The temperature of the water bath was reduced to 35 °C. Upon cooling, crystals of pulverized (*S*)-ibuprofen or racemic ibuprofen were added as a seed. The flask was placed in a water bath at 25 °C and the temperature was gradually reduced to 0 °C overnight in a refrigerator. Racemic ibuprofen crystals (0.13 g, 0.66 mmol, 6.8%) were collected by vacuum filtration and the methanol was evaporated from the filtrate to give 1.864 g (9.0 mmol, 93%) of (*S*)-ibuprofen with an ee of 99.7%. The specific rotation of this material was $[\alpha]_D^{25} = +59.5$ (*c* 1, ethanol 95%), indicating an ee of at least 99.2%. The melting point of 55 °C was in good agreement with the literature value of 55.5 °C.[16,17]

Acknowledgments

We gratefully acknowledge the financial support of the Department of Education of the State of Chihuahua (Mexico), the Department of Chemistry of the University of Texas at El Paso, the Graduate School and the College of Science of the University of Texas at El Paso, the US Army Research Laboratory, the Facultad de Ciencias Químicas de la Universidad Autónoma de Chihuahua and US Army Research Office (W911NF0410052), and the National Council of Science and Technology of Mexico (CONACyT).

References

1. Chavez-Flores, D.; James, M. S. *J. Biotechnol.* **2009**, *4*, 3.
2. Adams, S. S.; Blesslof, P.; Manson, G. C. *J. Pharm. Pharmacol.* **1976**, *28*, 2.
3. Reichel, C.; Brugger, R.; Bang, H.; Geisslinger, G.; Brune, K. *Mol. Pharmacol.* **1997**, *54*, 7.
4. Mustranta, A. *Appl. Microbiol. Biotechnol.* **1992**, *38*, 6.
5. Chen, C. Y.; Cheng, Y. C.; Tsai, S. W. *J. Chem. Technol. Biotechnol.* **2002**, *77*, 6.
6. Xin, J. Y.; Li, S. B.; Xu, Y.; Chui, J. R.; Xia, C. G. *J. Chem. Technol. Biotechnol.* **2001**, *76*, 7.
7. Lin, H. Y.; Tsai, S. W. *J. Mol. Catal. B: Enzymatic* **2003**, *24–25*, 9.
8. Cheng, Y. C.; Tsai, S. W. *Enzyme Microb. Technol.* **2003**, *32*, 7.
9. Xie, Y. C.; Liu, H. Z.; Chen, J. Y. *Biotechnol. Lett.* **1999**, *20*, 4.
10. Fazlena, H.; Kamaruddin, M.; Zulkali, M. *Bioprocess Biosyst. Eng.* **2006**, *28*, 7.
11. Ammazzalorso, A.; Amoroso, R.; Bettoni, G.; De Filippis, B.; Fantacuzzi, M.; Giampietro, L.; Maccallini, C.; Tricca, M. L. *Chirality* **2008**, *20*, 4.
12. Koops, B. C.; Verheij, H. M.; Slotboom, A. J.; Egmond, M. R. *Enzyme Microb. Technol.* **1999**, *25*, 10.
13. Van-Rantwijk, F.; Lau, R. M.; Sheldon, R. A. *Trends Biotechnol.* **2003**, *21*, 8.
14. Jayasundar, J.; Lakshmi, B.; Raviprasad, V.; Ananth, M.; Kangueane, P.; Gautam, P. *Protein Eng.* **2003**, *16*, 8.
15. Dzhanbaeva, N. R.; Rakhimov, M. M.; Yuldashev, P. Kh. *Chem. Nat. Compd.* **1972**, *10*, 4.
16. Jeffrey, P.; Gjhgnj, T. G.; Bye, A.; Crewe, H. K.; Wright, P. A. *J. Pharm. Pharmacol.* **1991**, *43*, 6.
17. Snell, D.; Colby, J. *Enzyme Microbial Technol.* **1999**, *24*, 160–163.